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WHAT WE SHOULD KNOW ABOUT MALARIAL DISEASE.

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MALARIAL HEMOGLOBINURIA.

Synonyms—Swamp Fever, Malarial Hematuria, Hemoglobinuric Fever, Hemorrhagic Pernicious Malaria, Bilious Hemoglobinuric Fever, Bloody Chills, Yellow Chills, Blackwater Fever, etc.

Definition—Marlarial hemoglobinuria is a syndrome appearing suddenly in persons harboring malarial infection for a protracted period, and characterized by a very severe chill, followed by red urine (from claret to pokeberry-juice color), fever, great prostration, nausea, vomiting, and very marked jaundice.

Hemolysis and hemoglobinuria associated with malaria has a pathology in some respects quite unique and not shared by other forms of malarial disease, nor by other conditions associated with hemolysis. Although we have in pernicious and chronic malaria some evidence of the presence of a soluble toxin, such as necrosis of red blood corpuscles, parenchymatous and fatty degenerations, focal necroses and multiple thromboses, we find in malarial hemoglobinuria all these phenomena markedly accentuated. The intense vomiting, biliousness, albuminuria and jaundice, are paralleled only in the second stage of yellow fever. Whereas, pernicious malaria manifests itself in many forms, according to which organ or set of organs is the seat of segmentation emboli, we are dealing with such conditions in hemoglobinuria, if they occur, only as complications. Here the vascular obstruction is inflammatory (thrombotic), blood destruction is in excess of the action of live plasmodia, which indeed soon disappear, and the entire symptom-complex is such as could not possibly be produced by the mere development of plasmodia, within red blood cells.

If malarial hemoglobinuria were nothing but acute pernicious fever, it could not strike persons weeks after return from the tropics, even to England, where malaria is not endemic. This disease is never a primary event. We have as a constant antecedent a prolonged harboring of malaria parasites in the blood or viscera, even though there be no evident symptoms. We rarely find it in persons with extremely large spleens, those whose blood and viscera are almost or entirely free of plasmodia: yet new-comers, who are such a ready prey to pernicious fevers, are absolutely immune to it. The relation to present infection will be alluded to later on. As to incidence with reference to term of residence, Brem reports one mild case within two months with a history of gross neglect. Plehn's 97 cases average three years, the earliest in three months (gross neglect emphasized). Daniels had four in the first six months out of 114 first attacks, and this is the experience of every observer. In regions where one season's sieges can be recovered from before the ravages of the next year begin, the disease is quite rare, or confined to imported cases. In yellow fever the greatest visceral intoxication, with degenerations, occurs only after the blood has ceased to be transmissible by mosquitos. In all diseases such pathologic phenomena appear late, when the intracellular poisons of the parasites must have been set free.

Let us see how malaria is acquired. The sporozoite, injected by the mosquito, is a wormlike body, having active vermicular motility, and can be seen to deliberately pierce a blood cell, enter, and develop into a schizont. The resulting embryos are spherical bodies having only brownian motility, and appear actuated by chemotaxis. They bound about, bump against blood cells, adhere to one, break loose again, become attached to others and finally sink through the rim of the corpuscle, completing their cycle to segmentation, exactly as the sporozoite has done. If all were to enter cells, the succeeding paroxysm would be 6 to 30-fold the severity of the first. Beginning with the breaking-up of the advance guard of a brood, and continuing for some hours after the last ones have segmented, the febrile paroxysm takes place. Assuming the plasma to be indifferent to the insoluble, non-functionating merozoites, the fever must be due to something else. It is not due to the growth of the nutritive bodies within the cells, because most of this takes place during the afebrile stage. There is much evidence to show that the residue of segmentation contains a plasma-soluble poison which causes the chill, fever and sweat. I believe, reasoning by analogy only, that this is a specific poison and is needed to sensitize red cells for invasion by the young merozoites. It is the opsonin needed by these spherical, non-motile, embryonic bodies to attract and attach them to the cell to be entered, not required by the sporozoites, who attack with their own weapons. In the normal scheme of defense we have phagocytosis, which can be seen in fresh malaria blood, probably also unsensitized corpuscles. Gradually, however, the individual acquires a resistance in addition to this. With repeated attacks the body depends more and more upon this developed new-formed resistance, and a condition of "latency" is established. New-comers are known not to have this resistance or defense of "latency;" every segmentation is followed by a paroxysm of fever; whereas, with old residents, this latency is quite the usual feature; an intercurrent factor, such as taking cold, a surgical operation, exposure, bad water, unhygienic living, eating watermelons, etc., usually brings on a chill quite suddenly and so coincidentally that old practitioners still find in it ground for rejecting the "mosquito theory."

Coming back to the biologic function of the parasite, the nutritive schizont within the cell grows at the expense of the hemoglobin, i. e., it now has a hemolytic function, which ceases and becomes latent again after segmentation, to become active only when the merozoite has entered a cell. It is hemolytic only in the growing stage when it lies safely within the corpuscle, and *when the patient is having no symptoms.* Golgi, working with unstained blood, taught, quite correctly, that quinine acted by preventing the invasion of red cells, but he was wrong in saying it killed the "spores." By the aid of modern staining methods we can observe in heavily cinchonized patients, filamentation, karyolysis and fragmentation of cytoplasm of the growing plasmodia, it arrests their development. If a cell containing such a parasite breaks up, unused endoplasmodial hemolysin is set free and, with the aid of the sensitizer, if unopposed by antibodies, it may lake cells *from without.* As a consequence, the spleen, through the portal vein, furnishes the liver with excess of hemoglobin, cadavers of cells and plasmodia, free poisons, etc., so that the hepatic cells are overworked and poisoned, and the patient becomes very "bilious." Sensitin and hemolysin* accumulate, adding to the hemoglobinemia, and the patient is "full of malaria." This is really latent hemoglobinuria. Any quinine now administered, by arresting the development of nutritive bodies and damaging (vide infra, Diessing's reaction) the infected cells, adds to the sum of free hemolytic elements, establishes a vicious circle and causes the explosion of a hemolytic paroxysm—active fulminant, instead of latent; there is, according to Koch "weiter nichts als eine Chinin Intoxikation," but a second dose, many times as large, if it happen not to meet nearly mature broods, appears to cure the patient. As Plehn points out, it would be absurd to say a minimal dose (¼ grain) would nearly kill a patient, when a subsequent manifold larger one has no such effect. As will be seen below, quinine is not necessarily nor exclusively the occasion for a hemolytic paroxysm.

It is not necessary to go into hair-splitting distinctions as to the character of hypothetical bodies, but certain hemolytic experiments made justify the belief that the soluble residue of segmentation is a specific opsonin having cytophilic affinities for red cells and that the endoplasmodial elements carry toxophore groups having hemolytic properties. Experiments with other hemolytic agents show that antibodies can be developed for either group, i. e., anti-amboceptors and anti-complements. The assumption that any auto-hemolytic function comes into play seems to me to be untenable, it being unparalleled in any scheme of defense.

So long, then, as the malaria remains more or less paroxysmal, and, possibly with the aid of the mechanism expressed as fever paroxysms, intervals occur during which these toxic substances may be eliminated and in part neutralized, and hemolysis with hemoglobinuria does not take place. The chance of their accumulating to the danger point is also minimized if the subject spends part of the year in a more salubrious region or has the protection of seasonal intermissions. This is just the difference in incidence and distribution between cyclic or paroxysmal malaria and blackwater fever. It accords with what was said in reference to incidence in the beginning of this article. The practice of only taking calomel for the "biliousness" merely postpones the evil day. Worse still is the practice of desultory, ill-timed or insufficient quinine taking, which throws all the work on this immunizing mechanism, the spleen and liver enlarge, the patient becomes sallow, has a coated tongue, and his blood, at least from the spleen, contains parasites, especially "female" ones, and, under the augmentation of reinfections, there is gradually developed an unstable defense, a "toxin fever" drives the patient to quinine or a patent chill tonic at a time when growing parasites are readily disturbed within necrobiotic cells, and—he has a chill, followed by "hematuria." Sometimes an intercurrent factor, or a fresh infection, is the occasion of the paroxysm, but in any case the quinine, the fresh infection, or the indifferent predisposing cause is only the *occasion* of the hemoglobinuric paroxysm and *not* the *specific cause.* The latter is always the "specific alteration of the blood," as Bignami expresses it in his vague hypothesis.

It has been taught, ever since the days of Binz, that quinine directly poisons the parasitic organism, since very weak solutions of it arrest ameboid movements of certain unicellular organisms. V. Diessing has ascertained that quinine only enters into a plasma-soluble combination (compound) with hemoglobin, which the parasites cannot metabolize and that they are thus starved. This harmonizes the old and new views and also explains why crescents are immune to quinine. This property of quinine undoubtedly plays a part in the cases called "quinine hemoglobinuria." It is erroneous to consider this as a separate and distinct disease because the two forms merge imperceptibly, and the quinine element is one of degree only. So far as I know, quinine hemolysis apart from prolonged malarial infection is unknown.

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*arbitrary names.

There is too much evidence in favor of quinine being, in the vast majority of cases, the "occasion" of the attack for any discussions to continue on this subject. For bibliography I refer to Deaderick, in the *Memphis Medical Monthly*, Dec., '07, *et seq.* The main thing I desire to make clear is that blackwater fever is produced by the disturbance of an unstable immunizing balance, that its primary effect on the infection is to minimize, if not abolish it, and that quinine, being a possible and most frequent provocator of it, should not be used or its use suspended until it can be ascertained if parasites persist or reactions to it no longer occur.

The rule that quinine therapy would be justified only when parasites are present is consequently not tenable. The presence of plasmodia is the very evidence of danger, although it may happen that in a given case there be no further reaction. I recall a case where the blood showed a very rich infection on the third day, after the urine had cleared up. This is just the condition in which even Plehn advises the exhibition of quinine. The attendant refused to give it and the expected fever paroxysm did not occur. What became of the plasmodia? I have myself had 28 cases recover who *never received another dose of quinine* after the first bloody urine. Is this pernicious malaria? Surely not. Some of these patients were extremely ill. Bearing upon this point, Stephens has grouped 219 cases with reference to the proportion having parasites at different stages. Those examined on the day before the attack showed 95.6 per cent. infected. Those examined on the day of the attack showed 61.9 per cent. with parasites, and of those examined on the day after the onset only 17.1 per cent. had plasmodia. This, and the differential leucocyte count shows that the disease is really malaria and that the blood rapidly becomes sterile. Again, Plehn has grouped, nearly equally, over 700 cases with reference to treatment. Those treated without quinine gave a mortality of about 15 per cent., as against over 17 per cent. for the quinine-treated cases.

A practical clinical division of varieties of malarial hemoglobinuria is the following: 1. Hemolytic pernicious fever; 2. hemolytic malarial cachexia; 3. malarial quinine hemolysis.

The first includes the cases occurring at the height of the season (where seasonal prevalence changes). As the re-infections are more common at this time, a larger percentage of this class of cases may have to be cinchonized, but not until after thorough purgation. The hemolytic paroxysm removes the element of urgency as to quinine. Those who die of "malaria" die in the first 24 hours, and are helpless under any system of treatment. The cases of this first class have the highest fever and the hemolytic reaction generally fails to completely kill off the plasmodia.

The cases of the second class come late, sometimes months after the wards have become emptied of the regular fever rush, are often spontaneous ("taking cold"), and are always to be treated without quinine until convalescence is well established. They have a lower temperature range unless renal symptoms are responsible for the fever.

The third class undoubtedly encompasses more complex factors. Although it plays a part in most cases because the "malaria in the system" has been the occasion for tinkering with quinine, it often persists as what appears to be a true post-malarial phenomenon. Generally the severity of the paroxysm is in definite proportion to the size of the dose. (Tomaselli's disease). It seems paradoxical that a drug can protect the corpuscles against invasion by live plasmodia, but not against the labile hemolysin, but we must remember that it is disturbing an immunizing process, introducing factors not readily solvable. We are less concerned with this phase of the subject than we are with the fact that the phenomena occur and have to be dealt with. The treatment is gradual immunization with small doses.

Skipping symptomatology, morbid anatomy and diagnosis for lack of space, we come to treatment. It can be seen by Plehn's statistics that in the hands of an experienced man the difference between the pro or con attiude as to quinine is small. If we had a simple and reliable test for the hemolytic reaction in a given case, quinine might turn the scale in a few cases. There is also some empyrical evidence in favor of the intramuscular method as against the internal administration. Considering that in this way it is more gradually absorbed and reaches the splanchnic circulation far more indirectly, there may be something in it. So long, however, as we have nothing but percentage data, we must still to some extent adhere to some rule-of-thumb. I believe the best rule is Plehn's: If before the hemoglobinuria there is a reaction to quinine by increased fever with progressive diminution of hemoglobin, its use should be suspended until other measures have been instituted. After hemoglobinuria has developed, quinine is suspended and tentatively resumed on the third day if a blood examination shows parasites to be then present. If, after the resumption of quinine, the urine becomes dark again, it must be stopped at once and later still more cautiously resumed. As soon as it induces no further reactions the blood is slowly but very completely saturated. This should be the routine during convalescence in all cases. If a case of the third class proves to have developed, arsenic is given and the quinine injected in very small doses at long intervals, or the patient sent to another climate. Reinfection must be carefully guarded against.

The Chloroform Treatment—This was introduced by Quennec in 1899. He reports 56 cases treated successfully by keeping the patient in a state of mild drunkenness with small doses of syrup of chloroform, frequently repeated. He claims for it that it renders quinine administration harmless, diminishes albuminuria, stops vomiting, produces diaphoresis and diuresis, establishes vaso-motor balance, and tranquilizes the patient. I have had nauseated patients object bitterly to its use; theoretically, it would seem to be contraindicated in the presence of much visceral degeneration.

The plan of management should be about as follows: During the chill (or rather rigor) administer chloroform emulsion; apply hot sinapisms to extremities, an icebag to the head and give pilocarpin, which is also sedative and usually finds its only chance at this stage. Several large doses of calomel without soda are given an hour apart, followed by sodium thiosulfate in hot water, until the black, tarry stools become fluid and yellow. If there is much vomiting, give hot drinks, which also tend to wash the stomach. If this fails, caffein, iodin, carbolic acid, cocaine or iced carbonated drinks should be tried. Avoid morphine, especially if there is much albuminuria or oliguria. If the purgatives are retained, the stomach is soon quieted. If the thiosulfate cannot be given, calomel, which is never completely vomited out, must be continued, but it is not necessary to resort to medieval barbarism in this respect. After this elimination of water through the stomach, bowels and skin, an effort must be made to replenish the body fluids through the same channels in the order named. A continuous hot saline colon irrigation (I use a catheter and a glass throttle to insure a slow current), with the patient on a pad and the bag scarcely above the level of the head, is the second routine step—at the end of the purgation, of course. Diuretics, turpentine, digitalis, morphine, ergot, quinine, and antipyretics are not to be used. Indeed, the medicinal treatment at this time is almost entirely symptomatic and expectant, and confined to the rectal or sub-cutaneous route. One cannot play heroics with degenerated organs, nor give cardiac stimulants to or greatly disturb the patient whose organs are full of thrombi; all active treatment is confined to the initial stage. These are routine directions, of course, and not iron-clad. The body surface must be covered and protected from air currents, even in hot weather, to prevent renal chills.

Uremia is a late symptom, and often wanting, even after days of anuria, because the kidney degeneration is acute and urotoxic elements have little chance to accumulate under active purgation. The anuria usually comes on suddenly, with hiccough. Nitrites, hot packs and hot colon flushes are used. Such barbarous measures as blisters, wet cups, leeches and moxa are still recommended! They are worse than useless. As the blood pressure rises and twitchings appear, apomorphine in minute, oft-repeated doses has served me well.

During convalescence arsenic and systemic tonics are needed, and, I repeat, the patient must be protected from reinfection, and, if at all possible, gradually but thoroughly saturated with quinine. If this cannot be done, he must be sent to non-malarious territory.

To those who insist on treating malarial hemoglobinuria with quinine, I have to give this parting warning: Give it intramuscularly and stop it if the fever rises or chills recur during its use. There is no malaria parasite which causes chills at intervals of a few hours or without some regularity, and there are no chills *during* remittent malaria—these are *not* malarial paroxysms, they are caused by the discharge of immature parasites into the plasmal. *Quinine positively aggravates such a condition.* Experienced "swamp doctors" give quinine during the height of a malarial fever only under conditions of extreme necessity, and never without misgivings.